

A METHOD FOR MAKING HETEROMULTIMERIC POLYPEPTIDES**ABSTRACT OF THE DISCLOSURE**

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The invention relates to a method of preparing heteromultimeric polypeptides such as bispecific antibodies, bispecific immunoadhesins and antibody-immunoadhesin chimeras. The invention also relates to the heteromultimers prepared using the method. Generally, the method involves introducing a protuberance at the interface of a first polypeptide and a corresponding cavity in the interface of a second polypeptide, such that the protuberance can be positioned in the cavity so as to promote heteromultimer formation and hinder homomultimer formation. "Protuberances" are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains (*e.g.* tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the protuberances are created in the interface of the second polypeptide by replacing large amino acid side chains with smaller ones (*e.g.* alanine or threonine). The protuberance and cavity can be made by synthetic means such as altering the nucleic acid encoding the polypeptides or by peptide synthesis.

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